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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,243	08/27/2001	James R. Baker JR.	UM-06609	6118

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EXAMINER	
BARHAM, BETHANY P	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/940,243	BAKER, JAMES R.	
	Examiner	Art Unit	
	Bethany P. Barham	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the Applicants' Response and Amended Claims and Information Disclosure Statement filed on 4/30/2007. Claims 26-46 are pending in this action. Claims 26-46 are rejected.

Applicants Arguments with respect to the art not teaching a reason for "changing the functional group from a reactive and highly positively charged amine terminated dendrimer to a neutral acetyl terminated dendrimer" was persuasive and the previous **rejections of record are herein modified** to provide art that does teach a reason.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-27, 29-31, 33-35, and 38-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 8-10, 22-23, and 27 of U.S. Patent No. 6,471,968 (herein referred to as '968) in view of Tomalia et al., *Angew. Chem. Int. Ed. Engl.* 29 (1990) p.138-175 (herein referred to as Tomalia et al),as further evidenced by Zhou et al, J. of Controlled Release (1999). Although claims 26, 39-40 and 45 are not identical to a single claim in '968, it is not patentably distinct from claims 1, 2 and 27 of '968. Both claim a composition comprising a dendrimer POPAM or PAMAM and that one dendrimer is covalently linked to another dendrimer with a functional group of a therapeutic agent. Both claim a composition with one or more functional groups selected from the group consisting of a therapeutic agent, a targeting agent, an imaging agent, or a biological monitoring agent. Both claim a therapeutic agent comprising a chemotherapeutic agent. Both claim a protecting group selected from photo-labile, radio-labile and enzyme-labile protecting groups. Both claim a composition with a chemotherapeutic agent selected from selected from platinum complex, verapamil, podophyllotoxin, carboplatin, procarbazine, mechlorethamine, cyclophosphamide, camptothecin, ifosfamide, melphalan, chlorambucil, bisulfan, nitrosurea, adriamycin, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicomycin, mitomycin, etoposide, tamoxifen, taxol, transplatinum, 5-fluorouracil, vincristin, vinblastin, and methotrexate. Both claim a nucleic acid attached to the dendrimer with a cleavage site comprising an enzyme.

Patent '968 does not claim an acetylated G5 dendrimer as claimed by Applicant. But '968 in view of Tomalia et al as evidenced by) and Zhou et al, J. of Controlled Release (1999), renders the instant claims further obvious because Tomalia et al teach that it is common to introduce reactive and passive chemical moieties on the surface of the dendrimer to change the functional groups either inside of on the dendrimer surface (p. 163, col. 1, last paragraph). Tomalia et al teach ester-terminated PAMAM (G0-G10), hydroxylated terminated PAMAM (G0-G9), ketone terminated PAMAM (-NHCOR for G0-G6), and many more (p. 163-167, also see Table 8 on p. 165). They teach that the different functional groups change the surfaces from hydrophilic to hydrophobic, anionic to cationic, etc. Changing the functional group from a reactive and highly positively charged amine terminated dendrimer to a neutral acetyl terminated dendrimer would be an obvious choice by one skilled in the art if one did not want the dendrimer reacting with surrounding negatively charged compounds and to become water soluble for drug/therapeutic delivery as evidenced by Zhou et al who specifically teaches acylation of dendrimers with acetic anhydride, which allows the dendrimer to become water soluble and linked to an active agent, with potential for a carrier as an antitumor drug (pg. 254-255, Conclusion).

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 26-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., *Angew. Chem. Int. Ed. Engl.* 29 (1990) p.138-175 (herein referred to as Tomalia et al) and Zhou et al, J. of Controlled Release (1999), in view of Malik et al., Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., 24 (1997) p. 107-108.

- Tomalia et al is taught above and teaches numerous functional groups attached to PAMAM dendrimers of various generations. Tomalia et al also teaches various NH2-terminated dendrimers reacted with either inorganic or organic acids and PAMAM dendrimer complexes formed from reactions with metals (p. 163-4, section 9.2.1-9.2.2). Tomalia et al teach conjugation of dendrimers to dopamine and catechol to act as targeting agents to increase ligand concentrations and conjugations to monoclonal antibodies for therapeutic and diagnostic purposes (p. 166-167, sections 9.2.5-9.2.6).
- Tomalia et al does not teach acylation of dendrimers, only functionalization.

- Zhou et al teaches that functionalizing dendrimers with various end groups that can be linked to other chemical moieties and enhance surface properties of dendrimers for drug carriers and gene transfer agents is well known in the art. Zhou et al specifically teaches acylation of dendrimers with acetic anhydride, which allows the dendrimer to become water soluble and linked to an active agent, with potential for a carrier as an antitumor drug (pg. 254-255, Conclusion).
- Tomalia et al and Zhou et al do not teach chemotherapeutic agents such as the platinum complex, cisplatin.
- The limitation of claim 32 is taught by Malik et al, who teaches that PAMAM dendrimers conjugated to the anti-tumor agent and platinum complex, cisplatin to form a dendrimer-Pt complex. The dendrimer-Pt complex was found to be effective in reducing toxicity and increasing water solubility of cisplatin, while still maintaining anti-tumor activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the chemotherapeutic agent, cisplatin into a PAMAM dendrimer with the functional groups as described by Tomalia et al and Zhou et al, since Tomalia teaches dendrimer metal complexes and Zhou et al teaches complexes with active agents (fluorouracil and antitumors). One of ordinary skill in the art would be motivated by the success of the results of Malik et al who found that the complexed dendrimer-Pt reduces toxicity and increases solubility of cisplatin to combine with the teachings of Tomalia et al. Thus, it would have been *prima facie* obvious to combine

the teaches of Malik et al with Tomalia et al and Zhou et al to obtain a drug containing dendrimer with the functional group of choice.

Claims 26-27 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., *Angew. Chem. Int. Ed. Engl.* 29 (1990) p.138-175 (herein referred to as Tomalia et al) and Zhou et al, J. of Controlled Release (1999), in view of US 5,714, 166 (herein referred to as '166).

- Tomalia et al is taught above, but does not teach fluorescent agents, specifically fluorescein isothiocyanate.
- Zhou et al is taught above, and teaches fluorescent agents such as fluorescein but not fluorescein isothiocyanate.
- The limitations of claims 36-37 are taught in '166. The conjugation of one or more functional groups (targeting and imaging agents) into dendrimers is taught. Specifically, example NN (col. 71 lines 40-42 and col. 72 lines 47-65) and example 29 (col. 91 line 9 – col. 92 line 14) teach preparation of PAMAM dendrimers conjugated to fluorescein isothiocyanate for imaging and various targeting agents.

It would have been obvious to one of ordinary skill in the art at the time the invention was made desiring to functionalize the surface of PAMAM dendrimers of various generations (G0-G9) to look to Tomalia et al. Tomalia et al teaches adding functional groups to the surface to change the surface charge. One of ordinary skill in the art would be motivated to obtain a neutral surface that would be less reactive with

biological compounds to look for a functional group that would impart the neutral charge and increase water solubility, such as the acetyl group as taught by Zhou et al. It would have been *prima facie* obvious to one of ordinary skill in the art that since PAMAM dendrimers are non-toxic and useful for specific delivery of imaging and targeting agents, and Zhou et al teaches that acylation and linkage to fluorescein is also non-toxic and useful for imaging, to look to the teachings '166 (the conjugation of PAMAM dendrimers to targeting and imaging agents, specifically fluorescein isothiocyanate) in conjunction with Tomalia et al and Zhou et al to obtain an acetylated PAMAM dendrimer for use in targeting and imaging in vitro.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bethany P. Barham whose telephone number is 571-272-6175. The examiner can normally be reached on M-F from 8:30am to 5pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bethany Barham
Examiner-1615

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